The Effect of Levetiracetam Treatment on Survival in Patients with Glioblastoma: A Systematic Review and Meta-Analysis.

Jia-Shu Chen (✉ jia-shu_chen@brown.edu)

The Warren Alpert Medical School of Brown University <https://orcid.org/0000-0002-4533-9476>

Ross Clarke

The Warren Alpert Medical School of Brown University

Alexander F. Haddad

UCSF: University of California San Francisco

Elaina J. Wang

The Warren Alpert Medical School of Brown University

Michel Lacroix

Geisinger: Geisinger Health

Indra Neil Sarkar

The Warren Alpert Medical School of Brown University

Ramin Zand

Geisinger: Geisinger Health

Elizabeth S. Chen

The Warren Alpert Medical School of Brown University

Steven A. Toms

Lifespan Health System

Research Article

Keywords: Anti-epileptic, Glioblastoma, Levetiracetam, Survival, Temozolomide

Posted Date: December 28th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-945912/v1>

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Version of Record: A version of this preprint was published at Journal of Neuro-Oncology on January 4th, 2022. See the published version at <https://doi.org/10.1007/s11060-021-03940-2>.

Abstract

Background:

Levetiracetam (LEV) is an anti-epileptic drug (AED) that sensitizes glioblastoma (GBM) to temozolomide (TMZ) chemotherapy by inhibiting O⁶-methylguanine-DNA methyltransferase (MGMT) expression. Adding LEV to the standard of care (SOC) for GBM may improve TMZ efficacy. This study aimed to pool the existing evidence in the literature to quantify LEV's effect on GBM survival and characterize its safety profile to determine whether incorporating LEV into the SOC is warranted.

Method:

A search of CINAHL, Embase, PubMed, and Web of Science from inception to May 2021 was performed to identify relevant articles. Hazard ratios (HR), median overall survival, and adverse events were pooled using random-effect models. Meta-regression, funnel plots, and the Newcastle-Ottawa Scale were utilized to identify sources of heterogeneity, bias, and statistical influence.

Results:

From 20 included studies, 5804 GBM patients underwent meta-analysis, of which 1923 (33%) were treated with LEV. Administration of LEV did not significantly improve survival in the entire patient population (HR=0.89, $p=0.094$). Significant heterogeneity was observed during pooling of HRs ($I^2=75\%$, $p<0.01$). Meta-regression determined that LEV treatment effect decreased with greater rates of MGMT methylation (RC=0.03, $p=0.02$) and increased with greater proportions of female patients (RC=-0.05, $p=0.002$). Concurrent LEV with the SOC for GBM did not increase odds of adverse events relative to other AEDs.

Conclusions:

Levetiracetam treatment may not be effective for all GBM patients. Instead, LEV may be better suited for treating specific molecular profiles of GBM. Further studies are necessary to identify optimal GBM candidates for LEV.

Introduction

Glioblastoma (GBM) is the most common and malignant primary tumor of the central nervous system [1]. The standard of care (SOC) for GBM involves cytoreductive surgery followed by adjuvant radiotherapy plus concomitant and maintenance temozolomide (TMZ) chemotherapy [2]. Despite an optimized protocol, GBM prognosis remains poor. Median overall survival (OS) is only ~15 months due to inevitable recurrence at ~7 months [2, 3]. Some trials for tumor treating fields (TTF) and vaccine immunotherapy have observed notable improvements in survival relative to the SOC [3-5]. However, long-term survival remains unchanged, with few (4%) surviving past five years [6, 7]. Furthermore, no additions to the SOC have been made despite many studies on diverse agents, highlighting the need for new therapeutic strategies [8].

The O⁶-methylguanine-DNA methyltransferase (MGMT) gene encodes a DNA-repair protein that abrogates the effects of TMZ by removing TMZ-induced alkyl groups from the O⁶-position of guanine, a site that triggers apoptosis when alkylated [9-11]. Methylation of the MGMT promoter causes epigenetic silencing of the gene and is associated with longer OS when present in GBM patients receiving TMZ [12]. Accordingly, MGMT methylation is a robust predictor of OS in GBM given its TMZ-enhancing effects [13]. However, methylation is not universal, with frequency ranging from 19-68% [14]. Given this variability, there is interest in identifying agents that can inactivate MGMT and be combined with TMZ to increase its anticancer potency [15, 16].

Levetiracetam (LEV) is a relatively new anti-epileptic drug that recently became one of the most commonly prescribed drugs for seizures in patients with brain tumors [17]. This trend is attributed to LEV's favorable pharmacokinetic profile that includes optimal bioavailability, minimal plasma protein binding, and faster steady-state concentrations, plus the fact that it does not induce cytochrome P450 enzymes, which degrade chemotherapeutics [18, 19]. However, clinical benefits of LEV may not be limited to seizure control. Studies have reported that LEV inhibits MGMT transcription in GBM via a p53-mediated corepressor complex of mSin3A and HDAC1 and enhances apoptosis with TMZ [20, 21]. Retrospective studies have shown promising survival benefits in GBM patients treated with LEV [22-24]. However, single-institution reviews are subject to biases from small sample sizes, patient selection, and variations in clinical practice that create non-generalizable results [25]. Furthermore, greater investigation has generated contrary findings, making it unclear whether LEV is a viable strategy [26]. Without a randomized controlled trial (RCT), a systematic review that pools the published evidence may provide the most clinical insight by mitigating limitations of retrospective studies and overcoming inter-study heterogeneity. Thus, this study was performed to systematically summarize the existing literature to: (1) determine whether LEV has a clinically generalizable survival impact and (2) describe the safety profile of LEV in patients with GBM.

Methods

This study was performed and is reported according to PRISMA guidelines under the supervision of an expert informatician (I.N.S.) with training in library and information science [27].

Search Strategy

A comprehensive literature search of CINAHL, Embase, PubMed, and Web of Science from inception to May 22nd, 2021 was performed using a search strategy designed with permutations of the following search terms and their variations: "Levetiracetam", "Glioblastoma", "Survival", and "Side Effect." The complete search strategy and its results are available in the **Supplementary Materials**.

Study Selection

Review of articles from the search strategy for inclusion occurred in two stages by two authors (J.C., R.C.) within Rayyan [28]. First, reviewers independently screened titles and abstracts of all articles to identify relevant studies. Duplicate articles were simultaneously screened and consolidated. Next, reviewers independently performed a full-text review of relevant studies using the criteria below to determine whether studies should proceed to meta-analysis. Cohen's kappa was calculated to evaluate strength of agreement, using the following thresholds for interpretation: <0.20 as slight, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial, and 0.81-1.00 as near perfect agreement [29].

Eligibility Criteria

Inclusion and exclusion criteria were established *a priori*. In order to include an article, the study needed to meet all of the following: (1) utilize case-control, cohort study, or RCT methodology; (2) focus on primary GBM patients; (3) stratify by LEV treatment; and, (4) report estimates describing survival outcomes or adverse events.

Articles were excluded if any of the following were met: (1) is a case report or review paper; (2) focuses on GBM cases not treated with surgery, recurrent GBM, or pediatric patients; (3) does not stratify by GBM diagnosis and LEV treatment; or, (4) does not report relevant outcomes on survival or adverse events. If a cohort was used to publish multiple studies on the same outcome, only the most complete report was included.

Data Extraction

Outcomes were abstracted from included studies by one author (J.C.). The following information was extracted when available: publication year, study design, number of patients treated with LEV, gender distribution, mean or median age at diagnosis, percentage of patients with MGMT methylation, percentage of patients who received gross total resection, TMZ, and the Stupp protocol, follow-up duration, hazard ratio (HR) comparing time-to-death between LEV and no LEV cohorts, median OS, and type and number of adverse events with LEV or other AED.

Quality Appraisal

The quality of each study was graded by one author (J.C.) using the Newcastle-Ottawa Scale (NOS) [30]. The NOS evaluates the quality and risk of bias by generating a quantitative score based on study type, selection of study cohort, comparability of participants, and adequacy of outcome metrics. A maximum score of 9 can be given, and the score was qualitatively categorized as poor (0-3), fair (4-6), or good (7+). Given the median survival with GBM under the Stupp protocol, adequate follow-up was defined as a mean or median follow-up of at least 15 months.

Statistical Analysis

Descriptive statistics were used to characterize the population of included articles. Categorical variables were reported using frequency and proportions. Continuous variables were described with median or mean and range. Pooling of HRs, difference in median survival, proportion of adverse events, and odds ratios (OR) was accomplished by using the inverse variance method for calculating weights and the DerSimonian-Laird random-effects modeling approach for estimating the overall study statistic to account for variability from clinical diversity and methodological variation between studies [31]. This was accomplished by assuming unequal variance and distributing statistical weighting more conservatively. Heterogeneity across studies was evaluated using the Higgins and Thompson's I^2 statistic, with an $I^2 \geq 75\%$ being considered significantly heterogenous [32]. Meta-regression was performed to identify potential sources of heterogeneity in the pooled data by analyzing how LEV treatment effect correlates with study year and design, age at diagnosis, gender, MGMT methylation, extent of resection, and adjuvant treatment regimen. Publication bias was evaluated using funnel plots of the treatment effect against variance and assessing for asymmetry. A two-tailed p -value < 0.05 was the threshold for statistical significance. All statistical analyses were performed in RStudio (RStudio, Inc., Version 1.2.1335).

Results

Study Selection

A total of 3509 citations were initially identified. After removing 927 duplicates, 2582 articles underwent title and abstract screening, of which 2340 were excluded. Full-text review of 242 studies led to the inclusion of 20 for meta-analysis. Two included articles reported findings using the same cohort of GBM patients [33, 34]. Both studies were included because one assessed survival outcomes [33], while the other detailed adverse events [34]. The sample size of these articles was only counted once. Interrater reliability was near perfect (Cohen's Kappa=0.82). The selection process is outlined in Figure 1.

Study Characteristics

The 20 included articles were published between 2006-2021, and their characteristics are listed in Table 1. Eleven (55%) were used to evaluate LEV's impact on survival [22-24, 26, 33, 35-40], while 12 (60%) were used to characterize the safety profile of administering LEV with the SOC in GBM [34, 37, 38, 41-48]. Most articles were retrospective observational cohort studies (60%). However, there were seven (35%) prospective studies, one that was a randomized trial with data on adverse events, and one that was a post-hoc analysis of RCTs for treatments unrelated to LEV. Overall, 5804 patients were included, of which 1923 (33%) received LEV.

Table 1
Characteristics of all included studies.

Study	Location	Study Design ^a	Cohort Size (LEV/no LEV)	Female (n, %)	Age (years)	MGMT Methylated (n, %)	GTR (n, %)	TMZ (n, %)	TMZ + RT (n, %)	FU (months)	Outcomes Reported
Barker (2013)	USA	R OCS (1)	531 (92/439)	189 (36%)	56 (18-70) ^b	NR	212 (40%)	185 (35%)	185 (35%)	NR	HR
Berendsen (2016)	Netherlands	R OCS (1)	647 (92/555)	260 (40%)	NR	NR	424 (66%)	NR	332 (51%)	NR	HR
Cardona (2018)	Colombia	P OCS (1)	213 (78/135)	92 (43%)	NR (17-84)	59 (28%)	136 (64%)	213 (100%)	213 (100%)	NR	AE; HR; mOS
Dinapoli (2009)	Italy	R OCS (1)	3 (3/0)	1 (33%)	64 (44-67) ^b	NR	2 (66%)	3 (100%)	1 (33%)	6 (6-6) ^b	AE
Fuller (2013)	Australia	P RCT (1)	13 (7/6)	NR	NR	NR	NR	NR	NR	NR	AE
Happold (2016)	Europe; NA	P RCT	1582 (541/1041)	644 (41%)	57 (18-82) ^b	750 (47%)	782 (49%)	1582 (100%)	1582 (100%)	NR	HR; mOS
Kim (2015)	Korea	R OCS (1)	103 (58/45)	51 (50%)	59 (18-84) ^b	28 (27%)	65 (63%)	103 (100%)	103 (100%)	17 (3-72) ^b	HR; mOS;
Knudsen-Baas (2016)	Norway	R OCS	1263 (195/1068)	532 (42%)	NR	NR	NR	721 (57%)	663 (52%)	NR	HR
Knudsen-Baas (2018)	Norway	R OCS	1263 (195/1068)	532 (42%)	NR	NR	NR	721 (57%)	663 (52%)	NR	AE
Knudsen-Baas (2021)	Italy; Norway	R OCS (3)	100 (71/29)	28 (28%)	54 (26-85) ^b	46 (46%)	48 (48%)	90 (90%)	89 (89%)	17 (3-145) ^b	AE; HR
Maschio (2006)	Italy	P OCS (1)	7 (7/0)	2 (29%)	63 (40-70) ^b	NR	1 (14%)	7 (100%)	0 (0%)	20 (9-31) ^b	AE
Maschio (2011)	Italy	P OCS (1)	9 (9/0)	4 (44%)	67 (44-75) ^b	NR	5 (56%)	9 (100%)	9 (100%)	NR	AE
Newton (2006)	USA	R OCS (1)	12 (12/0)	NR	NR	NR	NR	NR	NR	NR	AE
Rigamonti (2018)	Italy	R OCS (3)	235 (119/116)	89 (38%)	66 (28-83) ^b	NR	197 (69%)	176 (75%)	176 (75%)	37.2 (NR) ^b	HR
Roh (2020)	Korea	R OCS (1)	322 (169/153)	141 (44%)	58 (19-79) ^b	87 (29%)	171 (53%)	322 (100%)	322 (100%)	60.8 (NR) ^b	HR; mOS
Ryu (2019)	Korea	R OCS (1)	418 (322/96)	188 (45%)	57 (2-82) ^b	70 (17%)	NR	418 (100%)	418 (100%)	NR	AE; HR; mOS
Simo (2012)	Spain	P OCS (2)	101 (31/70)	32 (32%)	57 (NR) ^c	NR	49 (48%)	101 (100%)	101 (100%)	NR	HR; mOS
Toledo (2017)	Spain	P OCS (1)	56 (24/32)	24 (43%)	57 (30-77) ^c	NR	33 (59%)	56 (100%)	56 (100%)	NR	AE
Valko (2015)	Switzerland	P OCS (1)	65 (21/44)	21 (32%)	57.3 (NR) ^c	NR	14 (22%)	0 (0%)	0 (0%)	NR	AE

Abbreviations: *AE* Adverse Events; *CT* Clinical Trial; *FU* Follow-Up; *HR* Hazard Ratio; *GTR* Gross Total Resection; *IPD* Individual-Patient Data; *LEV* Levetiracetam; *mOS* Median Overall Survival; *NA* North America; *NR* Not Reported; *OCS* Observational Cohort Study; *P* Prospective; *R* Retrospective; *RCT* Randomized Clinical Trial; *RT* Radiotherapy; *TMZ* Temozolomide.

^aNumber of institutions involved in study reported in parentheses.

^bMedian (range)

^cMean (range)

Study	Location	Study Design ^a	Cohort Size (LEV/no LEV)	Female (n, %)	Age (years)	MGMT Methylated (n, %)	GTR (n, %)	TMZ (n, %)	TMZ + RT (n, %)	FU (months)	Outcomes Reported
Wychowski (2013)	USA	R OCS (1)	124 (72/52)	NR	NR	NR	37 (22%)	NR	NR	NR	AE
Abbreviations: <i>AE</i> Adverse Events; <i>CT</i> Clinical Trial; <i>FU</i> Follow-Up; <i>HR</i> Hazard Ratio; <i>GTR</i> Gross Total Resection; <i>IPD</i> Individual-Patient Data; <i>LEV</i> Levetiracetam; <i>mOS</i> Median Overall Survival; <i>NA</i> North America; <i>NR</i> Not Reported; <i>OCS</i> Observational Cohort Study; <i>P</i> Prospective; <i>R</i> Retrospective; <i>RCT</i> Randomized Clinical Trial; <i>RT</i> Radiotherapy; <i>TMZ</i> Temozolomide.											
^a Number of institutions involved in study reported in parentheses.											
^b Median (range)											
^c Mean (range)											

The majority of studies were graded as fair quality (70%), while four (20%) were good and two (10%) were poor. Of the studies evaluated for survival impact, all were fair (64%) or good (36%) quality. Investigations on survival tended to have high risk of bias because the length and/or adequacy of follow-up could not be confirmed and, to a lesser degree, because survival comparisons were confined to a subset of patients and not generalizable. Of the studies contributing safety data, all but one were fair (75%) or poor (17%) quality. Similarly, most studies on adverse events had high bias due to inadequate follow-up or because the study cohort was not representative of the GBM patient population. Detailed scoring outlining the NOS criteria for each study is reported in **Supplementary Table 1**.

Survival Meta-Analysis

Of the 11 studies included in the survival meta-analysis, three reported a significant improvement in survival [22-24], five suggested a trend towards improved survival [35-37, 39, 40], and one published significantly worse survival outcomes with LEV treatment [38]. Pooling results from all 11 studies led to a pooled HR of 0.89 (95%-CI=0.78-1.02) that trended towards significantly better survival in LEV patients ($p=0.094$). Significant heterogeneity was observed ($I^2=75\%$, $p<0.01$) during pooling (Figure 2A).

Median OS with 95%-CI was reported in six studies [22-24, 26, 37, 40]. The pooled median OS of the patients treated with LEV and no LEV was 22.9 (95%-CI=21.2-24.7) and 16.8 (95%-CI=15.1-18.6) months, respectively. The pooled difference in median OS between the LEV and no LEV treated cohorts was significant ($p<0.01$) and estimated to be 6.21 (95%-CI=2.75-9.66) months in favor of LEV treated patients. There was significant heterogeneity across the pooled studies ($I^2 = 100\%$, $p < 0.001$) (Figure 2B).

On meta-regression analysis, publication year (RC=0.10, 95%-CI=-0.06-0.08, $p = 0.75$), retrospective study design (RC=-0.14, 95%-CI=-0.47-0.18, $p=0.38$), age (RC=-0.03, 95%-CI=-0.11-0.04, $p=0.37$), gross total resection (RC=-0.01, 95%-CI=-0.03-0.01, $p=0.31$), and percentage of patients treated with the Stupp protocol (RC=-0.003, 95%-CI=-0.009-0.003, $p=0.30$) were not associated with LEV treatment effect. However, the percentage of MGMT methylated patients (RC=0.03, 95%-CI=0.01-0.05, $p=0.02$) and female patients (RC=-0.05, 95%-CI=[-0.08,0.02], $p=0.002$) were both significantly associated with LEV treatment effect (Figure 3A). A greater rate of methylation was associated with less significant and larger HRs, while a greater proportion of female patients was correlated with more significant and smaller HRs. A funnel plot for the pooling of HRs depicted a slight asymmetry suggestive of potential publication bias against insignificant results opposing LEV efficacy (Figure 3B).

Safety Meta-Analysis

From the 12 studies that reported data on adverse events, the most commonly reported complications were somnolence [41, 44-46], fatigue [37, 47, 48], neuropsychiatric disturbances [23, 34, 37, 38, 42, 46, 48], and allergic reactions and/or skin rashes [23, 37, 38, 42]. The proportion of patients encountering an adverse event from LEV while being treated for GBM was pooled and determined to be 23% (95%-CI=13-32%). The heterogeneity across studies was significant ($I^2=94\%$, $p<0.001$) (Figure 4A). The proportion of adverse events while being treated with LEV was compared to the proportion of complications under other AEDs, and the pooled OR was insignificant ($p=0.41$), with LEV having comparable odds of adverse events relative to other AEDs (OR=0.79, 95%-CI=0.45-1.38) (Figure 4B).

Discussion

Identification of effective treatments that can safely accompany and work in tandem with the SOC is essential for improving the prognosis of GBM. Thus, in this systematic review and meta-analysis, we assessed the published literature to determine whether LEV, an AED reported to improve GBM prognosis, prolongs survival for GBM patients in a safe and generalizable manner.

Pooling of published HRs demonstrated that LEV does not have a significant effect on survival. While there was a trend towards longer survival, the pooled treatment effect was not statistically significant. Our findings contrast those of a recent retrospective study and meta-analysis by Jabbarli *et al.* that reported a significant survival benefit but did not grade the quality of evidence, assess for potential sources of heterogeneity or bias, or

evaluate the safety of LEV with the SOC [49]. All the studies included in the aforementioned study were captured by our search strategy and selection process. However, we were also able to identify four additional investigations published between 2012-2021, two that were graded as “good” quality and two that were graded as “fair” [36, 38-40]. Of these four studies, none reported significantly improved survival, and one found LEV to be associated with significantly worse survival [38]. Furthermore, our assessment of publication bias using funnel plots indicated that results suggestive of LEV having an insignificant or deleterious impact on survival may be underreported. This was reaffirmed by two articles that found no survival benefit with LEV and were reviewed during our selection process but had to ultimately be excluded from meta-analysis because the authors did not report statistics that could be pooled [46, 50]. Thus, the treatment effect reported by Jabbarli *et al.*, and potentially this study, is likely overestimated and not as substantial as it is currently published for all patients with GBM.

While LEV may not have a survival impact on the entire GBM population, it is important to note that GBM is a highly heterogeneous disease with several distinct molecular subtypes that vary in gene expression, tumor mutational burden, epigenetic modifications, and, consequently, treatment responses [51-53]. Our meta-analysis highlighted this by concluding that there was significant heterogeneity across our pooled studies. To evaluate potential sources of heterogeneity, we performed meta-regression to identify any correlations between demographics and treatment effect and found that MGMT methylation and sex had a significant correlation. Specifically, populations with a lower rate of MGMT methylation or larger proportion of female patients had more robust differences in survival following LEV treatment.

In the original study reporting on the cellular effects of LEV on GBM, Bobustuc *et al.* found that LEV enhances tumor cell apoptosis to TMZ by inhibiting MGMT expression. Given this mechanism of action, LEV's therapeutic efficacy may be enhanced in patients who are not methylated at the MGMT promoter, since those who are methylated will already have lower MGMT expression and experience the survival benefit associated with it [12]. Furthermore, sex differences in GBM incidence and survival are well reported, with being female consistently found to be associated with lower incidence and better outcome [54, 55]. More importantly, however, investigations into the potential mechanisms behind these sex differences have highlighted that increased incidence of GBM, tumorigenesis, and poor treatment responses in males is attributed to sexual dimorphism in the p53 pathway, specifically greater TP53 mutational burden and increased susceptibility to deregulated X-linked genes that negatively regulate p53 in males [56, 57]. The second main finding in Bobustuc *et al.*'s original study was that LEV's inhibition of MGMT expression is dependent on the expression of p53, mSin3A, and HDAC1, meaning patients with reduced p53 viability, such as males, may not be positioned to experience the benefits of LEV treatment, as seen in our findings.

These results may highlight the potential limitations of LEV as a therapeutic modality; however, they do not encourage the abandonment of LEV as a therapy worth investigating. Instead, this study highlights the importance of first identifying the GBM patient population who should be actively sought out and targeted for adjuvant LEV treatment, in addition to those with epileptic seizures, before conducting an RCT as has been previously encouraged so that adequate controls and study designs are implemented to account for LEV's mechanism of action. Biomarker-driven patient selection is becoming increasingly important in the study design of clinical trials to ensure accurate conclusions, especially in a disease like GBM that is not only very heterogeneous but has also experienced many clinical trial failures [58, 59]. With our current trajectory towards greater utilization of personalized oncology treatments and molecular diagnoses, LEV could still have great potential for treating GBM even if only certain populations benefit, especially given its safety profile that was confirmed to be acceptable alongside the SOC in this study. Further studies correlating molecular and genomic data with the clinical effect of LEV are needed to confirm the trends identified in this study and ensure that a robust RCT study design is undertaken to truly determine whether LEV improves survival.

This review had several limitations. Although an exhaustive search strategy was designed and utilized, it is possible that relevant studies were not identified due to screening errors or inappropriate indexing. While most studies were “fair” or “good” quality, scores were most commonly marked down due to an inability to confirm the adequacy of follow-up. Given this, treatment effects may have been improperly estimated because too many patients were lost to follow-up or not followed for the appropriate duration. Furthermore, the topic of follow-up underscores another significant limitation known as protopathic bias. In this situation, a patient treated with LEV and another without may have had similar biological survival from tumor initiation to time of death. However, the patient with LEV may be documented as having longer clinical survival because their need to control seizures with LEV may have caused earlier diagnosis. Finally, while our study determined that MGMT methylation correlated with reduced LEV treatment effect, there is likely heterogeneity across studies in how methylated and unmethylated patients were categorized given that there is no universally-accepted test or consensus cut-off for MGMT status [60]. Future prospective studies will need to ensure that there is adequate follow-up, consistent MGMT status determination criteria, and properly matched and randomized patients.

Conclusion

This systematic review and meta-analysis determined that LEV can be safely delivered with the SOC for GBM but does not significantly improve survival in all patients. However, there was significant heterogeneity across studies, and meta-regression demonstrated that certain populations may benefit from LEV. Investigations using molecular and genetic sequencing data to identify patients most likely to benefit from LEV are needed to determine what additional populations with GBM should be actively considered for LEV treatment.

Declarations

Disclosures: No financial disclosures or conflicts of interest to report.

Author Contributions:

Conception and Design: Jia-Shu Chen, Steven A. Toms; Acquisition of Data: Jia-Shu Chen, Ross Clarke; Statistical Analysis and Interpretation of Data: Jia-Shu Chen, Ramin Zand, Steven A. Toms; Drafting the Article: Jia-Shu Chen; Critical Review of the Article: All Authors; Approved Final Version of Manuscript: All Authors; Administrative/Technical/Material Support: Michel Lacroix, Indra Neil Sarkar, Ramin Zand, Elizabeth S. Chen, Steven A. Toms; Study Supervision: Steven A. Toms.

Conflicts of Interests

The authors report no conflicts of interest or funding sources concerning the materials and methods used in this study or the results and findings detailed in this paper.

Data Availability

The datasets generated and analyzed in the current study are available from the corresponding author on reasonable request.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent

Informed consent was not required due to study design requiring no collection of data other than from the published literature.

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Figures

Figure 1

PRISMA flow diagram of search results and study selection.

Figure 2

Forest plots of the meta-analysis comparing survival between LEV and no LEV treatment using: (A) Hazard Ratios and (B) The difference in median overall survival.

A.

B.

C.

Figure 3

Evaluation of sources of heterogeneity and publication bias using: Meta-regression analysis of LEV treatment effect with **(A)** percentage of MGMT methylated patients and **(B)** female sex as the moderator variable, and **(C)** Funnel plot of reported LEV treatment according to the standard error.

A.

B.

Figure 4

Forest plots of the meta-analysis evaluating the safety profile of LEV treatment in GBM using: (A) The pooled prevalence of adverse events during LEV treatment and (B) The pooled odds ratio comparing the likelihood of adverse events with LEV treatment as opposed to other AED treatment.

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